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Early View

Original article

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Oxygen compared to air during exercise training in COPD with exercise-induced desaturation

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Take home message:

Exercise training improved exercise capacity and quality of life in normoxaemic COPD patients who demonstrated oxygen desaturation during exercise, with no greater improvement with supplemental oxygen during exercise training compared to air.

INTRODUCTION

Pulmonary rehabilitation is an important component of the management of people with chronic obstructive pulmonary disease (COPD) with strong evidence of efficacy (1). Clinically significant improvements in exercise capacity, breathlessness, fatigue and health-related quality of life (HRQoL) are consistently documented in randomised controlled trials of pulmonary rehabilitation that include an exercise training component (1). Exercise-induced oxygen desaturation is common among people with COPD, with up to 47 % of patients referred to pulmonary rehabilitation demonstrating a decrease in oxygen saturation measured by pulse oximetry (SpO_2) to less than 90% during a field walking test (2, 3). Patients who desaturate may not tolerate high intensity exercise (4) and healthcare professionals may strive to minimise exercise-induced desaturation by decreasing training intensity and/or imposing mandatory rests. This reduction in exercise intensity is likely to limit the effectiveness of training (5).

Physiological studies have demonstrated that supplemental oxygen during an acute bout of exercise reduces minute ventilation at equivalent work rates and delays the onset of dynamic hyperinflation and associated dyspnoea (6-9), thus augmenting exercise capacity in people with moderate to severe COPD (9, 10). Therefore, supplemental oxygen may enable higher exercise intensity during an exercise training program (11, 12) and is often provided for people with COPD during exercise training, especially those who desaturate during exercise (13). However, there is limited evidence to support the provision of supplemental oxygen in clinical practice. Previous randomised trials comparing oxygen and air during exercise training have had small sample sizes (14-16), and included those on long-term oxygen therapy (LTOT) (15) and non-desaturators (11, 17). Stronger evidence to support or refute the

use of supplemental oxygen during pulmonary rehabilitation for people with COPD who are normoxaemic at rest but who desaturate during exercise is therefore required.

The aims of the study were to determine, in people with COPD who were normoxaemic at rest and desaturated during exercise, whether supplemental oxygen during exercise training was more effective than medical air (sham intervention) in: 1) improving endurance exercise capacity and HRQoL; and 2) improving peak walking capacity, reducing dyspnoea and increasing levels of daily physical activity. We hypothesised that those receiving oxygen would have greater increases in exercise capacity and HRQoL at completion of the exercise training program than those receiving medical air.

METHODS

This study was a prospective, multi-centre, randomised controlled trial with concealed allocation, and blinding of participants, trainers and assessors. The full protocol has been published previously (18). In brief, participants with a confirmed diagnosis of COPD on spirometry (19) with nadir SpO_2 < 90% from the better of two six-minute walk tests (6MWT) performed on room air (20) were recruited from referrals to pulmonary rehabilitation at seven participating sites. The study was approved by the Ethics Committees of all participating sites and registered with the Australian New Zealand Clinical Trials Registry: ACTRN 12612000395831. Informed written consent was obtained from all participants.

Randomisation with stratification for study site, six-minute walk distance (6MWD) (≤350 meters vs >350 meters) and nadir SpO_2 from the 6MWT (nadir SpO_2 89-86% vs < 86%) into an Oxygen Group or Air Group was by a central independent telephone randomisation

system and only decoded at the completion of the statistical analyses. Participants, exercise trainers and assessors were blind to group allocation. Concentrators (5L NewLife Elite Oxygen Concentrator, AirSep Corporation, Buffalo, New York) were identical in appearance whether they delivered oxygen or air. Internal modification of the concentrator to deliver medical air for the Air Group was undertaken by the supplier (Air Liquide, HealthCare Pty Ltd, Sydney, Australia) with approval from the Therapeutic Goods Administration, Australia, and the code was only available to the randomisation centre. Both groups received gas flow of 5 litres/minute via nasal prongs during exercise training.

Exercise training for both groups initially consisted of 20 minutes of treadmill walking at 80% of average 6MWT speed and 10 minutes of stationary cycling at 60% of the peak work rate, estimated from the 6MWT (21), supervised three times per week for eight weeks. Exercise duration was progressed up to a total of 40 minutes (20 minutes treadmill walking and 20 minutes stationary cycling) by week three. Throughout the training program, work rate (intensity) was increased according to symptoms so that dyspnoea or rate of perceived exertion (RPE) was at a 'moderate' to 'somewhat severe' level (i.e. a score of 3 to 4 on the modified dyspnoea and RPE 0-10 scales) (22).

The SpO_2 was monitored during one training session each week by a clinician independent of the study and blind to group allocation. The level of SpO_2 was not revealed to the trainer and training was interrupted only if the SpO_2 fell below 80% (23). The participant was asked to recommence exercising when SpO_2 returned to 88%. The independent clinician recorded the duration of exercise and rests, which was reproduced by the trainer for the remainder of the sessions in that week.

At the end of the exercise training program participants were provided with an education booklet and an individualised home maintenance exercise program. No domiciliary supplemental oxygen was provided during the training or in the 6-month home program.

Outcome measures

The primary outcomes were endurance exercise capacity measured by the endurance shuttle walk test (ESWT) (24) and HRQoL measured by the Chronic Respiratory Disease Questionnaire (CRQ)-Total (25). The secondary outcomes were peak exercise capacity measured by the incremental shuttle walk test (ISWT) (26), the domain scores of the CRQ, (i.e Dyspnoea, Fatigue, Emotional function, Mastery), severity and impact of dyspnoea using the Dyspnoea-12 Questionnaire (27) (in which a lower score indicates less dyspnoea), and physical activity levels measured by a multi-sensor activity monitor (SenseWear MF, BodyMedia, Pittsburgh USA) worn for seven days. The minimum wear time for inclusion of physical activity data was set at three days for at least 20 hours per day. All outcome measures were taken at baseline, at the completion of exercise training and six months following completion of the exercise training program. The ESWT and ISWT were performed twice at each of these measurement timepoints.

Sample size calculation

An estimated 110 participants were needed to ensure that 88 participants completed the study, allowing for a 20% loss to follow-up. This sample size was sufficient to provide 80% power to detect as significant, at the (two-sided) 5% level, a minimum 156 second difference (28) in the mean ESWT time between the Oxygen Group and the Air Group, assuming a standard deviation (SD) of 250 seconds for the ESWT (29) and to detect a minimum 0.5 point difference (30) in the mean CRQ-Total points per item between the groups, assuming a SD of

0.85 points per item (31).

Data analysis

The exercise training dose that each participant achieved was calculated from the product of the training intensity and exercise duration (32). The training intensity was estimated using the American College of Sports Medicine equations for walking and leg cycling (33) and expressed as metabolic equivalents (METs). For walking, the training dose calculation included speed, grade and session duration, and for cycling included power and session duration. Training dose was then expressed as METs completed per session for each participant.

Data were analysed using SPSS Version 22 (IBM New York, USA) on an intention-to-treat basis. Differences between groups for change over time were analysed using linear mixed models. Models included intervention group, time (i.e data collection time-points of baseline, end-training, six months after completion of training), group x time interaction and random effect. Baseline values were included as a covariate. Uncertainty regarding the mean between-group differences was quantified with 95% confidence intervals. Baseline and end-training dyspnoea and RPE from the ESWT were compared at isotime, defined as the end time of the shortest test used in analysis. Participants who completed a minimum of 16 training sessions (66% of total sessions) were included in a *per protocol* analysis using the same methods as the primary analysis.

RESULTS

Participant flow and characteristics

One hundred and eleven participants were recruited with 58 randomised to the Oxygen Group

and 53 to the Air Group (Figure 1). Participants, on average, had severe COPD (mean (SD) FEV_1 46 (17) % predicted, FEV_1/FVC ratio 0.43 (0.13)) (Table 1). At baseline Oxygen and Air groups were similar for lung function, arterial blood gases and 6MWD. The baseline, end-training and 6-month follow-up values for all outcomes for both the Oxygen and Air groups are reported Table 2.

Table 1: Participant characteristics

Variable	Oxygen Group *n* = 58	Air Group *n* = 53	Loss to follow up *n* = 14
Age, years	69 (7)	69 (8)	65 (8)
Gender, male/female	30/28	31/22	8/6
BMI, kg/m^2	27 (6)	29 (7)	29 (8)
Current smokers, n (%)	2 (3)	4 (8)	0 (0)
Pulmonary function			
FEV_1, L	1.2 (0.4)	1.2 (0.5)	1.1 (0.2)
FEV_1, % predicted	47 (17)	45 (16)	42 (8)
FVC, L	2.9 (1.0)	2.9 (0.9)	2.8 (0.7)
FVC, % predicted	83 (19)	79 (15)	78 (14)
FEV_1/FVC, %	42 (11)	43 (14)	41 (9)
RV/TLC, %	55 (9)	54 (10)	54 (7)
D_LCO, % predicted	48 (17)	50 (16)	57 (21)
GOLD grade			
I, n (%)	2 (3)	1 (2)	0 (0)
II, n (%)	16 (28)	18 (34)	3 (21)
III, n (%)	31 (53)	24 (45)	10 (71)
IV, n (%)	9 (16)	10 (19)	1 (8)
Arterial Blood Gases, room air			
pH	7.4 (0.03)	7.4 (0.04)	7.4 (0.02)
PaO_2, mmHg	70.5 (10)	73.9 (12)	73.0 (7)
$PaCO_2$, mmHg	37.8 (5)	37.5 (4)	40.8 (5)
SaO_2, %	94 (4)	94 (2)	94 (2)
6 min walk distance, m	401 (108)	402 (97)	414 (100)
SpO_2 nadir, (%)	85 (4)	85 (4)	86 (3)
CRQ-D average score, baseline	3.2 (1)	2.9 (1)	3.2 (1)
Dyspnoea-12 score, baseline	15 (9)	17 (9)	16 (7)
Co-morbidities			
Hypertension, n (%)	14 (24)	26 (49)	7 (50)

Cardiac (including previous surgery), n (%)	14 (24)	19 (36)	4 (29)
Diabetes, n (%)	11 (19)	5 (9)	2 (14)
Bronchiectasis, n (%)	2 (3)	5 (9)	2 (14)
Other respiratory history, n (%)	4 (7)	8 (15)	1 (7)
Cancer history, n (%)	8 (15)	4 (8)	2 (14)
Neurological, n (%)	3 (5)	4 (8)	2 (14)
Psychological, n (%)	2 (3)	8 (15)	2 (14)
Increased cholesterol, n (%)	14 (24)	10 (19)	4 (29)
Musculoskeletal, n (%)	19 (33)	19 (36)	4 (29)

Data presented as mean (SD) unless stated otherwise. BMI: body mass index; CRQ-D: chronic respiratory disease questionnaire dyspnoea domain; D_L,CO: single breath diffusing capacity for carbon monoxide; FEV_1: forced expiratory volume in 1second; FRC: functional residual capacity; FVC: forced vital capacity; pH: potential of hydrogen; kg: kilograms; kg/m^2: kilograms per meter squared; L: litre; m: metres; n: number; %: percent; PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide; RV: residual volume; SpO_2: oxygen saturation;TLC: total lung capacity.

Table 2: Exercise capacity, health-related quality of life, Dyspnoea-12 and physical activity at baseline, end training and 6-month follow-up

		Baseline		End-training		6-month	
		Oxygen group	Air Group	Oxygen group	Air Group	Oxygen group	Air Group
ESWT	n	58	53	51	44	38	36
	Time, seconds	327 (191)	319 (139)	500 (361)	456 (308)	423 (307)	423 (328)
	n	51	44	51	44		
	Dyspnoea isotime, score	4.3 (1.8)	4.8 (1.7)	3.3 (1.7)	3.7 (1.7)		
	RPE isotime, score	3.7 (2.2)	4.5 (2.1)	2.7 (1.9)	3.1 (2.1)		
ISWT	n	58	53	50	44	39	36
	Distance, metres	287 (121)	285 (124)	326 (128)	304 (132)	335 (137)	311 (124)
	n	50	43	50	43		
	Dyspnoea isotime, score	3.4 (1.6)	3.6 (1.7)	2.6 (1.4)	3.2 (1.4)		
CRQ	n	58	53	52	45	42	36
	Total score, ppi	4.3 (0.8)	4.1 (1.0)	4.7 (0.9)	4.6 (0.9)	4.7 (0.9)	4.6 (1.0)
	Dyspnoea, ppi	3.2 (1.0)	2.9 (1.0)	3.8 (1.2)	3.5 (1.1)	3.8 (1.3)	3.5 (1.3)
	Fatigue, ppi	4.0 (1.1)	3.5 (1.3)	4.5 (1.1)	4.2 (1.3)	4.3 (1.2)	4.2 (1.3)
	Emotional Function, ppi	4.8 (1.1)	4.8 (1.2)	5.2 (1.1)	5.0 (1.2)	5.1 (1.2)	5.1 (1.1)
	Mastery, ppi	5.0 (1.2)	5.0 (1.4)	5.3 (1.2)	5.4 (1.2)	5.5 (1.1)	5.2 (1.3)
Dyspnoea-12	n	58	53	52	45	42	36
	Total, score	15 (9)	17 (9)	13 (9)	17 (9)	14 (8)	17 (9)
	Physical, score	11 (6)	12 (6)	9 (5)	11 (6)	10 (5)	12 (5)
	Affective, score	5 (4)	5 (5)	4 (4)	5 (5)	5 (4)	5 (5)
Physical activity	n	56	47	48	39	36	29
	Steps per day, n	3032 (2074)	3158 (2374)	3138 (2225)	2903 (2002)	3215 (2172)	3852 (2915)
	Total EE/day, kcal	2089 (421)	2195 (459)	2037 (401)	2247 (418)	2079 (414)	2214 (545)
	Sedentary, min/day	731 (163)	785 (154)	756 (146)	775 (172)	738 (169)	760 (160)
	Light: min/day	215 (128)	180 (107)	176 (102)	159 (84)	210 (135)	193 (97)
	Moderate: min/day	26 (33)	25 (31)	26 (31)	26 (33)	25 (27)	29 (33)
	Vigorous: min/day	3 (10)	2 (6)	2 (5)	3 (9)	2 (4)	2 (4)

Data presented as mean (SD). CRQ: chronic respiratory disease questionnaire; ESWT: endurance shuttle walk test; ESWT Dyspnoea isotime score: comparison of dyspnoea scores at the end time of the shortest ESWT; ISWT Dyspnoea isotime score: comparison of dyspnoea scores at the end time of the shortest ISWT; ISWT: incremental shuttle walk test; METs: metabolic equivalents; min:minutes; ppi: points per items; RPE: rate of exertion; Sedentary: Awake time spent METs <1.5; Light Activity: Time spent METs 1.5 to <3; Moderate Activity: Time spent METs 3 to <6; Vigorous Activity: Time spent METs ≥6; min/day: minutes per day.

Primary outcomes

For the change in ESWT time, there was no between-group difference at end-training (Table 3, Figure 2A). Within-group analyses at end-training showed significant improvements in ESWT time in both the Oxygen and Air groups (Table 3). There was no between-group difference in the change in CRQ-Total score at end-training (Table 3, Figure 2B). Within-group analyses at end-training showed that both the Oxygen Group and the Air Group had significant improvements in CRQ-Total (Table 3).

At 6-month follow-up, there were no between-group differences in change in ESWT time or CRQ-Total (Table 3, Figure 2A&B). Within group analyses showed non-significant improvements in ESWT from baseline to 6-month follow-up in both Oxygen and Air groups. There were significant within-group increases in CRQ-Total from baseline to 6-month follow-up in both the Oxygen and Air groups (Table 3).

Secondary outcomes

There was no between-group difference in the change in incremental shuttle walk distance (ISWD) at end-training (Table 3). The within-group analysis at end-training showed significant improvements in ISWD in both Oxygen and Air groups (Table 3). There were no between-group differences in the change in any CRQ domain scores at end-training (Table 3). There were significant within-group improvements at end-training in both the Oxygen and Air groups in CRQ-Dyspnoea, CRQ-Fatigue and CRQ-Mastery, with the improvements in CRQ-Dyspnoea and CRQ-Fatigue exceeding the minimal important difference of 0.5 points (34) in both groups (Table 3). CRQ-Emotional function was only significantly improved in the Oxygen Group at end-training.

There were no between-group differences in change in Dyspnoea-12 scores at end-training. Significant within-group improvements in Dyspnoea-12 Total and Dyspnoea-12 Physical were only evident in the Oxygen Group (Table 3). For change in physical activity, there were no significant between-group or within-group differences at end-training in any physical activity outcomes (Table 3).

There were no significant between-group differences in change in dyspnoea or rate of perceived exertion (RPE) at isotime in the ESWT. Within-group analyses showed that dyspnoea and RPE were significantly lower at ESWT isotime in the Oxygen and Air groups at end-training (Table 3).

There were no between-group differences in the change in any secondary outcomes from baseline to 6-month follow-up (Table 3). Within-group changes in the Oxygen Group showed a significant increase in ISWD and significantly greater scores in CRQ-Dyspnoea, CRQ-Fatigue and CRQ-Mastery from baseline to 6-month follow-up (Table 3). In the Air Group, CRQ-Total, CRQ-Dyspnoea and CRQ-Emotional function were significantly greater from baseline to 6-month follow-up (Table 3).

TABLE 3: Within-group and between-group statistical analyses

		Within-group differences from baseline (95% CI)				Between-group differences	
		Oxygen Group		Air Group		Oxygen - Air	
		End-training	6-month	End-training	6-month	End-training	6-month
ESWT	Time, seconds	162 (80 to 244)*	76 (-16 to 169)	147 (59 to 235)*	91 (-4 to 187)	15 (-106 to 136)	-15 (-148 to 118)
	Dyspnoea isotime, score	-1.2 (-1.6 to -0.8)*		-0.9 (-1.4 to -0.4)*		-0.3 (-0.3 to 0.9)	
	RPE isotime, score	-1.2 (-1.7 to -0.7)*		-1.1 (-1.6 to -0.5)*		-0.2 (-0.6 to 0.9)	
ISWT	Distance, metres	33 (20 to 47)*	24 (9 to 39)*	28 (13 to 42)*	15 (-1 to 30)	5 (-14 to 25)	9 (-12 to 31)
	Dyspnoea isotime	-0.9 (-1.2 to -0.5)*		-0.3 (-0.7 to 0.1)		-0.6 (-1.2 to -0.1)#	
CRQ	Total, ppi	0.4 (0.2 to 0.7)*	0.3 (0.1 to 0.5)*	0.4 (0.2 to 0.7)*	0.4 (0.1 to 0.6)*	0.0 (-0.3 to 0.3)	-0.0 (-0.4 to 0.3)
	Dyspnoea, ppi	0.7 (0.4 to 1.0)*	0.6 (0.3 to 0.9)*	0.6 (0.3 to 0.9)*	0.6 (0.3 to 0.9)*	0.1 (-0.3 to 0.5)	0.004 (-0.5 to 0.5)
	Fatigue, ppi	0.6 (0.3 to 0.9)*	0.3 (0.01 to 0.7)*	0.5 (0.2 to 0.9)*	0.3 (-0.01 to 0.7)	0.03 (-0.4 to 0.5)	-0.01 (-0.5 to 0.5)
	Emotional Funct, ppi	0.4 (0.1 to 0.6)*	0.2 (-0.0 to 0.5)	0.2 (-0.0 to 0.5)	0.3 (0.01 to 0.6)*	0.2 (-0.2 to 0.5)	-0.1 (-0.4 to 0.3)
	Mastery, ppi	0.3 (0.0 to 0.5)*	0.3 (0.0 to 0.6)*	0.3 (0.1 to 0.6)*	0.1 (-0.2 to 0.4)	-0.1 (-0.5 to 0.3)	0.2 (-0.2 to 0.6)
Dyspnoea-12	Total, score	-2.3 (-4.0 to -0.5)*	-0.7 (-2.6 to 1.2)	-0.3 (-2.2 to 1.6)	0.2 (-1.8 to 2.3)	-1.9 (-4.5 to 0.7)	-0.9 (-3.7 to 1.9)
	Physical, score	-1.5 (-2.7 to -0.4)*	-0.5 (-1.8 to 0.7)	-0.3 (-1.6 to 0.9)	0.7 (-0.7 to 2.0)	-1.2 (-2.9 to 0.5)	-1.2 (-3.1 to 0.6)
	Affective, score	-0.8 (-1.6 to 0.1)	-0.2 (-1.2 to 0.7)	0.1 (-0.8 to 1.0)	-0.4 (-1.4 to 0.6)	-0.9 (-2.2 to 0.4)	0.2 (-1.2 to 1.6)
Physical Activity	Steps per day, n	57 (-277 to 391)	146 (-233 to 524)	-283 (-654 to 87)	462 (34 to 889)*	340 (-157 to 839)	-316 (-887 to 255)
	Total EE/day, kcal	-35 (-109 to 40)	-55 (-139 to 29)	24 (-58 to 107)	-51 (-147 to 45)	-59 (-171 to 53)	-4 (-132 to 125)
	Sedentary, min/day	7 (-24 to 38)	12 (-23 to 46)	-10 (-44 to 25)	-13 (-52 to 26)	16 (-30 to 63)	25 (-27 to 77)
	Light: min/day	-27 (-47 to -8)	-1 (-23 to 22)	-21 (-43 to 1)	8 (-17 to 34)	-6 (-36 to 24)	-9 (-43 to 25)
	Moderate: min/day	3 (-3 to 8)	-3 (-9 to 3)	-0 (-6 to 6)	-1 (-8 to 6)	3 (-6 to 11)	-2 (-11 to 8)
	Vigorous: min/day	-1 (-2 to 1)	-1 (-3 to -0)	0 (-1 to 1)	-1 (-2 to 1)	-1 (-2 to 1)	-1 (-3 to 1)

Data presented as mean and 95% CIs adjusted for baseline values. *significant within group difference from baseline; # significant between group difference

CRQ: chronic respiratory disease questionnaire; EE: energy expenditure; ESWT: endurance shuttle walk test; Funct: Function; ISWT: incremental shuttle walk test; ESWT Dyspnoea isotime score: comparison of dyspnoea scores at the end time of the shortest ESWT; ISWT Dyspnoea isotime score: comparison of dyspnoea scores at the end time of the shortest ISWT; METs: metabolic equivalents; min/day: minutes per day; n: number; ppi: points per item; RPE: rate of perceived exertion; Sedentary: awake time spent METs <1.5; Light: time spent METs 1.5 to <3; Moderate: time spent METs 3 to <6; Vigorous: time spent METs ≥6.

Exercise training

During the exercise training program, both groups increased the training dose per session for treadmill and cycle training (Figure 3). There was no between-group difference in mean training dose over the 24 training sessions for treadmill exercise (mean difference 2.2 total METs [-5.0 to 9.3] favouring oxygen group). For cycle exercise, the Oxygen Group had a significantly greater mean training dose than the Air Group (mean difference 4.1 total METs [0.2 to 8.0]).

Data collected by the independent clinician showed that mean SpO_2% for each group in the last five minutes of the 20 minute training session for treadmill and cycle exercise was significantly higher in the Oxygen Group than the Air Group (mean difference [95%CI] 5% (4 to 6) for treadmill and mean difference [95%CI] 3% [1 to 4] for cycle (Table 4). Exercise training was only interrupted in four participants for SpO_2 < 80%, one in the Oxygen Group and three in the Air Group, and none were interrupted during cycle training. The mean dyspnoea and RPE scores during training were 3-4 ('moderate' to 'somewhat severe') at each training session for both the Oxygen and Air groups (Table S1). Dyspnoea and RPE scores were significantly higher in the Air Group than the Oxygen Group during treadmill training. RPE scores were significantly higher in the Air Group than the Oxygen Group during cycle training (Table S1). Spirometric indices remained stable over the eight months of the study (Table S2).

Table 4: Oxygen saturation during treadmill and cycle exercise training

	Oxygen Group Mean (SD)	Air Group Mean (SD)	Between-group differences Oxygen – Air Mean diff (95% CI)
Treadmill, SpO_2%	94 (3)	89 (4)	5 (4 to 6)
Cycle, SpO_2%	94 (3)	92 (3)	3 (1 to 4)

Data are the average weekly measures of percent oxygen saturation (SpO_2%) in all participants in the last 5 minutes of the 20 minute treadmill and cycle exercise training.

The incidence and severity of adverse events were similar in both groups. In the Oxygen Group one participant developed atrial fibrillation during a training session, one had a syncopal episode on the way to a training session and there was one death unrelated to the study. In the Air Group, one participant had a mild stroke after finishing a treadmill training session and one participant had a minor heart attack on a non-training day.

Per protocol analyses

Eighty-nine participants (48 Oxygen Group and 41 Air Group) attended at least 16 training sessions and therefore met the criteria for inclusion in per protocol analyses (Table S3, S4 and S5). Similar to the results of the intention-to-treat analyses, there were no between-group differences in changes from baseline in any of the outcomes at end-training or at 6-month follow-up. There were significant within-group changes in exercise capacity and HRQoL in both groups (Table S5).

DISCUSSION

Supplemental oxygen used during an 8-week supervised exercise training program resulted in no greater improvements in endurance exercise capacity or HRQoL than did medical air in people with COPD who desaturated during a 6MWT. Importantly, both the Oxygen and Air groups achieved benefits after exercise training, with significant increases in both exercise capacity and HRQoL as would be expected in an effective exercise training program in people with COPD (1).

Our results augment those of previous studies that compared exercise training with supplemental oxygen or air but which had less methodological rigor, including lack of

blinding (2, 14-16, 35), small sample sizes (14-16), higher SpO_2 criteria for stopping exercise (e.g. exercise training stopped if SpO_2 fell below 90%) (14, 16), training sessions of short duration (15),the inclusion of participants on LTOT (15) or provision of oxygen for home exercise (2), all of which impact the interpretation of findings. However, as in our study, most studies reported no significant between-group differences in exercise capacity (2, 14-16) or HRQoL (2, 14, 15) at the end of an exercise training period where participants used either supplemental oxygen or air during training. One study (35) reported a significantly greater walk distance after training in an oxygen group compared to an air group, however, the outcome exercise test was performed on oxygen in the oxygen group and on air in the air group, making the significant between-group difference difficult to interpret.

Based on the acute physiological responses to oxygen during exercise in people with moderate to severe COPD (8, 9, 36) it might have been expected that the Oxygen Group would have been able to train at a higher intensity than the Air Group, and that this would confer greater improvements in exercise capacity (32). However, during treadmill training the Oxygen Group were not able to achieve a greater training dose per session than the Air Group despite a significantly higher measured SpO_2 and significantly lower dyspnoea and RPE scores during treadmill training sessions. This was likely the reason for an absence of between-group differences in change in exercise capacity measured by a walking test at end-training. The fact that a higher SpO_2 did not confer greater training benefits in the Oxygen Group may be due to the large physiological stimulus applied to both groups, (i.e training three times per week for eight weeks at an increasing exercise dose). This training stimulus likely overwhelmed the small physiological advantage of acute oxygen administration that would have been expected to favour the Oxygen Group.

Importantly, both Oxygen and Air groups achieved the benefits in exercise capacity and HRQoL that would be expected from an exercise training program in people with COPD (1), with reductions in CRQ-Dyspnoea and CRQ-Fatigue which met or exceeded the minimal important differences of 0.5 (34) in both groups at end-training. Such findings show that the exercise training program was sufficiently intense to elicit improvements in this specific group of patients who desaturated during exercise and that these improvements could be achieved without supplemental oxygen. At 6-month follow-up the improvement in CRQ-Dyspnoea in both groups still exceeded the minimal important difference, demonstrating a strong effect of exercise training in both groups on this important patient-reported outcome. Although there were improvements in exercise capacity in both groups, these did not translate into increases in physical activity in either group. This finding is consistent with a recent systematic review (37) that found little evidence that exercise training improves daily physical activity levels in people with COPD.

This was a large, rigorously blinded, randomised controlled trial of oxygen versus air during training in COPD, in which the exercise training program was representative of programs commonly provided in pulmonary rehabilitation (38), participants were not stopped due to desaturation, and in which the primary outcome measure, the ESWT, was reflective of daily life. Such features make the study methods and findings applicable to most pulmonary rehabilitation programs. The loss to follow-up at end of training was small (13%), further strengthening these findings. However, there were a number of limitations. While stratification by minimisation was used for variables of 6MWD and nadir SpO_2 to ensure equivalence of groups at baseline, the acute response to oxygen supplementation was not evaluated. Therefore, there may have been an imbalance between the groups of oxygen responders (i.e. those who increase exercise performance while breathing oxygen) and non-

responders (39). As no baseline characteristics have been shown to predict oxygen response (40), it was not possible retrospectively to determine whether groups were similar for this variable. Nonetheless, randomisation should have ensured a similar number of oxygen responders in both groups. Since the study was not powered to evaluate the effects of oxygen supplementation compared to medical air during training in people with severe oxygen desaturation (i.e SpO_2 of $\leq 80\%$ during a 6MWT) the findings cannot be generalised to this group, or to those prescribed LTOT, those with other lung diseases such as interstitial lung disease, or those with pulmonary hypertension.

In summary, this large randomised controlled trial with blinding of participants, trainers and assessors found that both Oxygen and Air groups significantly improved exercise capacity and HRQoL with no greater benefit from training with supplemental oxygen than with medical air. The clinical implication from this study is that supplemental oxygen to correct oxygen desaturation is not required for patients to benefit from exercise training. Thus, for people with COPD, who are normoxaemic at rest but who desaturate during exertion, exercise training programs could be provided in venues where supplemental oxygen is not available, enabling pulmonary rehabilitation programs to be more widely accessible in the community.

Word Count: 3,118

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Figure 1: Flow of participants through the trial. SpO_2: oxygen saturation; 6MWT: six-minute walk test; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; mmHg: millimeters of mercury; DNA: did not attend

Figure 1

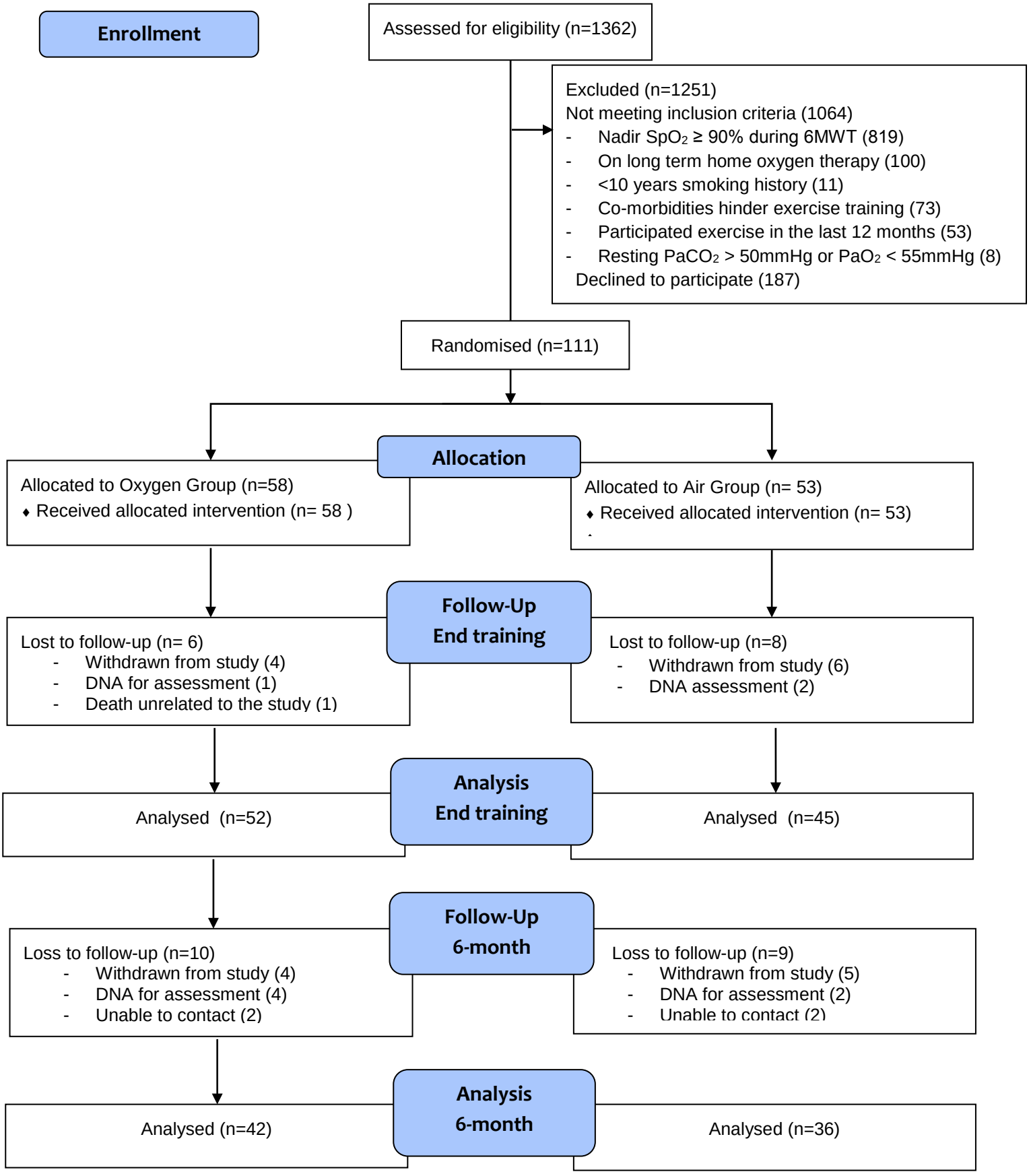
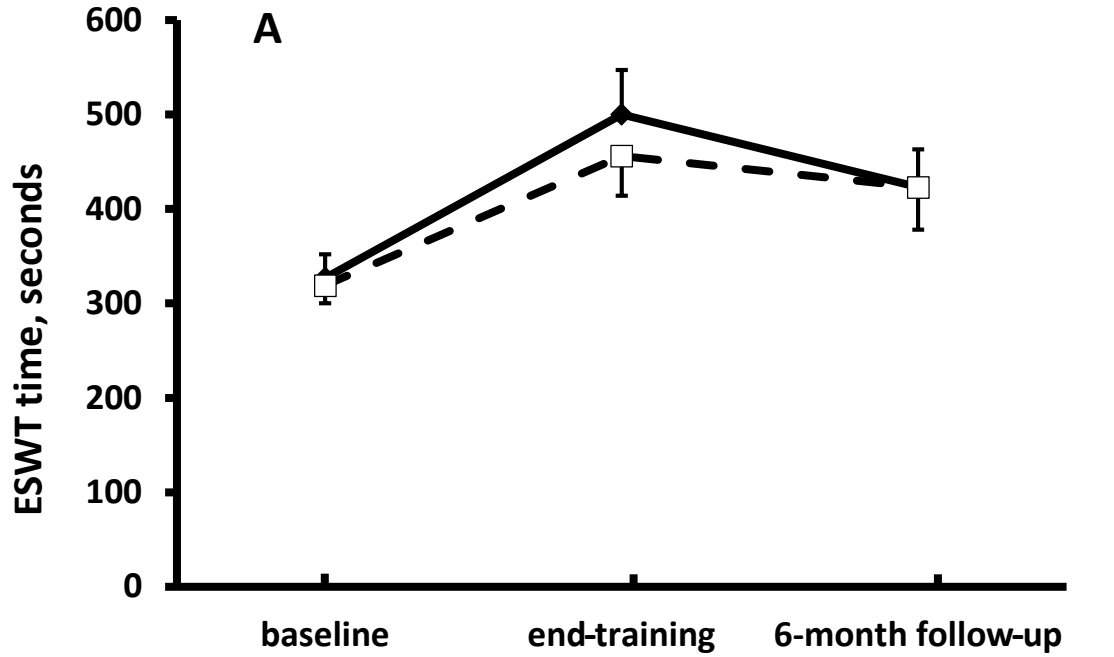

Enrollment
Assessed for eligibility (n=1362)
Excluded (n=1251)
Not meeting inclusion criteria (1064)
- Nadir SpO_2 ≥ 90% during 6MWT (819)
- On long term home oxygen therapy (100)
- <10 years smoking history (11)
- Co-morbidities hinder exercise training (73)
- Participated exercise in the last 12 months (53)
- Resting $PaCO_2$ > 50mmHg or PaO_2 < 55mmHg (8)
Declined to participate (187)
Randomised (n=111)
Allocation
Allocated to Oxygen Group (n=58)
♦ Received allocated intervention (n= 58)
Allocated to Air Group (n= 53)
♦ Received allocated intervention (n= 53)
Follow-Up
End training
Lost to follow-up (n= 6)
- Withdrawn from study (4)
- DNA for assessment (1)
- Death unrelated to the study (1)
Lost to follow-up (n=8)
- Withdrawn from study (6)
- DNA assessment (2)
Analysis
End training
Analysed (n=52)
Analysed (n=45)
Follow-Up
6-month
Loss to follow-up (n=10)
- Withdrawn from study (4)
- DNA for assessment (4)
- Unable to contact (2)
Loss to follow-up (n=9)
- Withdrawn from study (5)
- DNA for assessment (2)
- Unable to contact (2)
Analysis
6-month
Analysed (n=42)
Analysed (n=36)

Figure 2: Change in endurance shuttle walk test time in the Oxygen Group and the Air Group (A) and change in chronic respiratory questionnaire (CRQ)-Total in the Oxygen Group and the Air Group (B). Oxygen Group ——◆—— ; Air Group – –□– – ; ppi: points per item; error bars: standard error

Figure 2


A
600
500
400
300
200
100
0
ESWT time, seconds
baseline
end-training
6-month follow-up

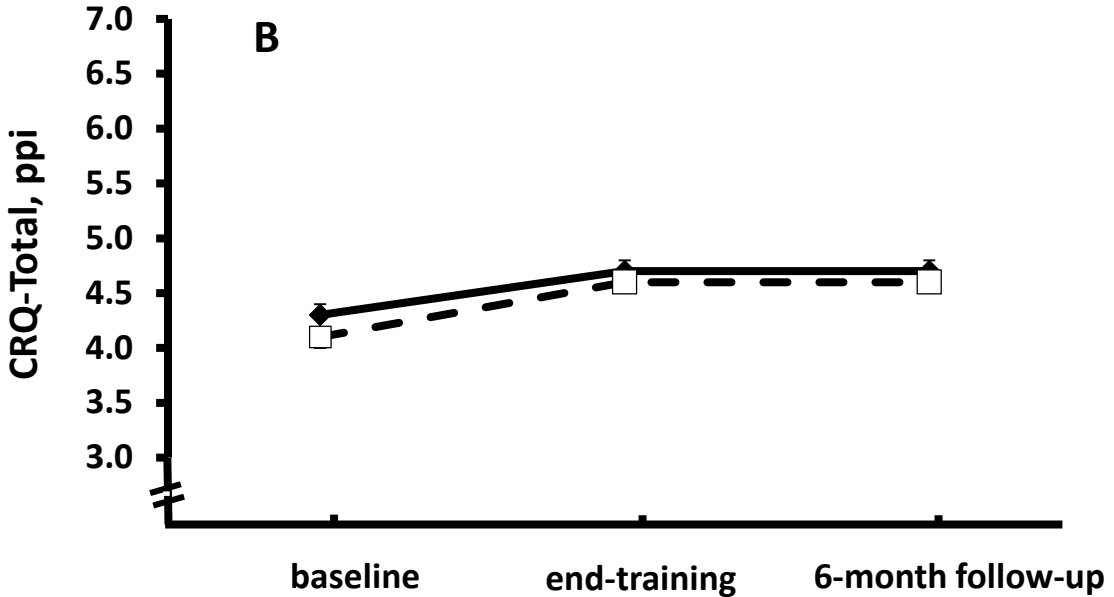

B
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
CRQ-Total, ppi
baseline
end-training
6-month follow-up

Figure 3: Mean total work (duration x METs) per training session for the Oxygen Group —◆— and Air Group – –□– – for treadmill exercise (A) and cycle exercise (B). METs: metabolic equivalents; error bars: standard error

Figure 3

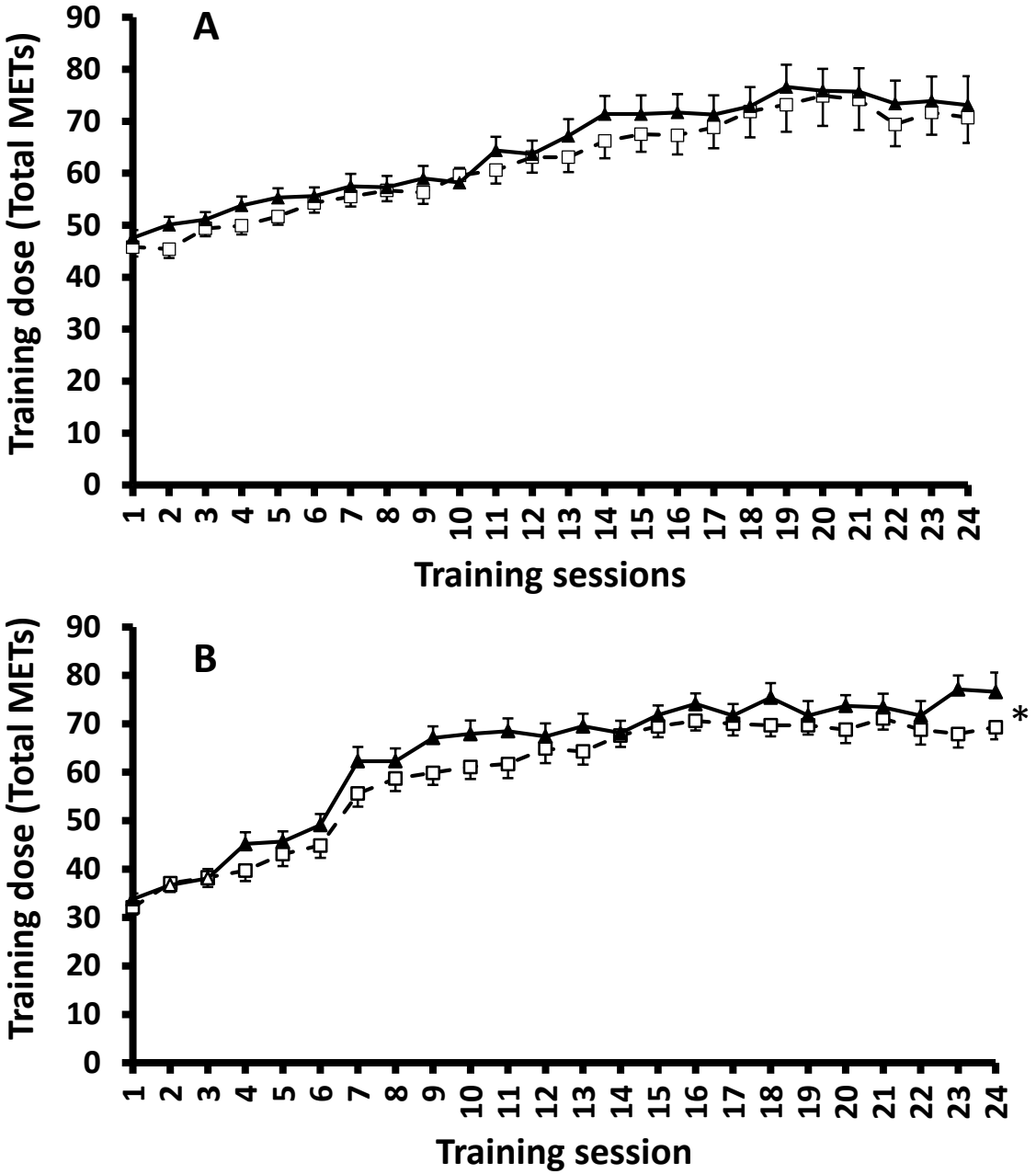

A
Training dose (Total METs)
0
10
20
30
40
50
60
70
80
90
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Training sessions
B
Training dose (Total METs)
0
10
20
30
40
50
60
70
80
90
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Training session
*

Table S1: Dyspnoea, rate of perceived exertion (RPE) scores and oxygen saturation during training

	Treadmill training			Cycle training		
	Oxygen Group Mean (SD)	Air Group Mean (SD)	Mean diff (95%CI)	Oxygen Group Mean (SD)	Air Group Mean (SD)	Mean diff (95%CI)
Dyspnoea	3.2 (1.1)	3.7 (1.3)	0.58 (0.10 to 1.07)	3.4 (1.1)	3.5 (0.9)	0.09 (-0.23 to 0.51)
RPE	3.1 (1.1)	3.9 (1.2)	0.81 (0.34 to 1.28)	3.5 (1.1)	4.0 (1.0)	0.48 (0.07 to 0.89)

Data are the mean (SD) of each training session for all participants in the Oxygen or air Group. Statistical analysis used linear mixed model to calculate the mean difference and 95%CI. RPE: rate of perceived exertion.

Table S2: Spirometry at baseline, end-training and 6-month follow-up for combined Oxygen and Air groups

FEV_1, litres			FVC, litres		
Baseline	**End-training**	**6-month**	**Baseline**	**End-training**	**6-month**
1.07 (0.41)	1.11 (0.43)	1.09 (0.43)	2.57 (0.83	2.62 (0.84)	2.58 (0.78)

Data are mean (SD). FEV_1: forced expiratory volume in one second; FVC: forced vital capacity

TABLE S3: Participant characteristics of participants attending a minimum of 16 training sessions and those who did not attend at least 16 training sessions.

Variable	Oxygen Group *n* = 48	Air Group *n* = 41	Oxygen Group *n* = 4	Air Group *n* = 4
	Attended ≥ 16 sessions		Attended < 16 sessions	
Age, years	70 (6)	69 (7)[#]	69 (10)	77 (5)
Gender, male/female	26/22	23/18	0/4	3/1
BMI, kg/m^2	27 (6)	30 (6)	25 (10)	25 (7)
Current smokers, n (%)	2 (4)	4 (10)	0 (0)	0 (0)
Pulmonary function				
FEV_1, L	1.2 (0.4)	1.2 (0.5)	1.1 (0.3)	1.2 (0.6)
FEV_1, % predicted	47 (17)	45 (17)	54 (28)	48 (20)
FVC, L	3.0 (1.0)	3.0 (0.9)	2.2 (0.4)	2.9 (1.3)
FVC, % predicted	84 (18)	79 (15)	85 (28)	81 (28)
FEV_1/FVC, %	42 (12)	43 (15)	47 (7)	44 (18)
RV/TLC, %	55 (10)	54 (11)	51 (9)	57 (9)
D_LCO, % predicted	49 (17)	48 (15)	32 (1)	58 (9)
6 min walk distance, m	408 (111)	402 (96)	314 (87)	343 (37)
SpO_2 nadir, (%)	85 (3)	85 (4)	82 (2)	85 (4)

#Significant difference in Air Group between those who attended ≥ 16 sessions and those who attended < 16 sessions

BMI: body mass index; D_L,CO: single breath diffusing capacity for carbon monoxide; FEV_1: forced expiratory volume in 1second; FVC: forced vital capacity; kg: kilograms; kg/m^2: kilograms per meter squared; L: litre; m: metres; n: number; %: percent RV: residual volume; SpO_2: oxygen saturation; TLC: total lung capacity.

TABLE S4: Exercise capacity, health-related quality of life, Dyspnea-12 and physical activity data at baseline, end-training and 6-month follow-up for participants who attended ≥ 16 sessions

		Baseline		End-training		6-month	
		Oxygen Group	**Air Group**	**Oxygen Group**	**Air Group**	**Oxygen Group**	**Air Group**
ESWT	n	48	41	48	41	37	34
	Time, s	348 (202)	308 (126)	497 (354)	466 (314)	426 (310)	405 (211)
	Dypsnoea isotime, score	4.3 (1.8)	4.8 (1.8)	3.3 (1.7)	3.8 (1.7)		
	RPE isotime, score	3.8 (2.1)	4.5 (2.2)	2.7 (1.9)	3.2 (2.1)		
ISWT	n	48	41	47	41	38	34
	Distance, m	296 (125)	280 (119)	331 (128)	310 (135)	336 (138)	303 (142)
	Dyspnoea isotime	3.3 (1.5)	3.6 (1.6)	2.5 (1.5)	3.2 (1.4)		
CRQ	n	48	41	48	41	40	34
	Total, ppi	4.3 (0.8)	4.1 (1.0)	4.8 (0.8)	4.6 (0.9)	4.7 (0.9)	4.6 (1.0)
	Dyspnoea, ppi	3.2 (1.0)	2.8 (1.0)	4.0 (1.1)	3.5 (1.2)	3.8 (1.3)	3.5 (1.3)
	Fatigue, ppi	3.9 (0.9)	3.6 (1.2)	4.6 (1.0)	4.3 (1.2)	4.3 (1.2)	4.2 (1.2)
	Emotional Funct, ppi	4.8 (1.0)	4.8 (1.2)	5.3 (1.1)	5.1 (1.2)	5.1 (1.2)	5.2 (1.1)
	Mastery, ppi	5.1 (1.2)	5.0 (1.4)	5.5 (1.2)	5.4 (1.2)	5.6 (1.0)	5.2 (1.3)
Dyspnoea-12	n	48	41	48	41	40	34
	Total, score	15 (9)	17 (9)	13 (8)	17 (9)	14 (9)	17 (8)
	Physical, score	10 (6)	12 (6)	9 (5)	11 (5)	10 (5)	12 (5)
	Affective, score	5 (4)	5 (5)	4 (4)	5 (5)	5 (4)	5 (5)
Physical activity	n	47	37	45	36	34	28
	Steps per day, n	3131 (2106)	3301 (2417)	3279 (2226)	3028 (2025)	3297 (2168)	3766 (2931)
	Total EE/day, kcal	2080 (395)	2217 (422)	2061 (404)	2248 (434)	2099 (404)	2212 (555)
	Sedentary, min/day	735 (163)	791 (153)	749 (164)	775 (178)	737 (162)	767 (159)
	Light: min/day	214 (126)	172 (87)	181 (100)	159 (87)	203 (125)	188 (95)
	Moderate: min/day	24 (30)	26 (33)	27 (32)	26 (34)	25 (28)	28 (33)
	Vigorous: min/day	3 (8)	2 (5)	2 (4)	3 (9)	2 (4)	1 (3)

Data presented as mean (SD). CRQ: chronic respiratory disease questionnaire; ESWT: endurance shuttle walk test; Isotime: comparison of isotime score at baseline and end training; ISWT: incremental shuttle walk test; METs: metabolic equivalents; min:minutes; RPE: rate of exertion;

Sedentary:Awake time spent METs <1.5; Light Activity: Time spent METs 1.5 to <3; Moderate Activity: Time spent METs 3 to <6; Vigorous Activity: Time spent METs ≥6; min/day: minutes per day.

Table S5: Within-group and between-group statistical analyses for participants who attended ≥ 16 sessions

		Within-group differences from baseline (95% CI)				Between-group differences	
		Oxygen Group		Air Group		Oxygen - Air	
		End-training	6-month	End-training	6-month	End-training	6-month
ESWT	Time, seconds	152 (69 to 234)*	72 (-20 to 163)	153 (64 to 243)*	76 (-20 to 172)	-2 (-124 to 120)	-5 (-138 to 129)
	Dyspnoea isotime, score	-1.2 (-1.7 to -0.4)		-0.9 (-1.4 to -0.4)		-0.3 (-1.0 to 0.3)	
	RPE isotime, score	-1.3 (-1.8 to -0.7)*		-1.1 (-1.7 to -0.5)*		-0.2 (-0.9 to 0.6)	
ISWT	Distance, metres	32 (19 to 46)*	23 (9 to 38)*	30 (16 to 44)*	10 (-5 to 25)	2 (-18 to 22)	13 (-8 to 34)
	Dyspnoea isotime, score	-0.9 (-1.3 to -0.5)*		-0.3 (-0.7 to 0.1)		-0.6 (-1.2 to -0.0)#	
CRQ	Total, ppi	0.6 (0.4 to 0.8)*	0.4 (0.2 to 0.6)*	0.5 (0.2 to 0.7)*	0.4 (0.2 to 0.7)*	0.1 (-0.2 to 0.4)	-0.0 (-0.4 to 0.3)
	Dyspnoea, ppi	0.8 (0.5 to 1.1)*	0.7 (0.4 to 1.0)*	0.6 (0.3 to 0.9)*	0.6 (0.3 to 1.0)*	0.2 (-0.2 to 0.6)	0.0 (-0.4 to 0.5)
	Fatigue, ppi	0.7 (0.4 to 1.0)*	0.5 (0.1 to 0.8)*	0.6 (0.3 to 1.0)*	0.4 (0.1 to 0.7)*	0.1 (-0.4 to 0.5)	0.0 (-0.4 to 0.5)
	Emotional Funct, ppi	0.5 (0.2 to 0.7)*	0.3 (0.0 to 0.5)*	0.3 (-0.0 to 0.5)	0.3 (0.0 to 0.6)*	0.2 (-0.2 to 0.6)	-0.1 (-0.5 to 0.3)
	Mastery, ppi	0.4 (0.1 to 0.6)*	0.4 (0.1 to 0.7)*	0.4 (0.1 to 0.6)*	0.1 (-0.2 to 0.4)	0.0 (-0.4 to 0.4)	0.2 (-0.2 to 0.7)
Dyspnea-12	Total, score	-2.4 (-4.1 to -0.6)*	-0.8 (-2.7 to 1.1)	0.1 (-1.8 to 2.0)	0.5 (-1.5 to 2.6)	-2.5 (-5.1 to 0.1)	-1.3 (-4.1 to 1.4)
	Physical, score	-1.6 (-2.7 to -0.4)*	-0.6 (-1.8 to 0.7)	-0.1 (-1.4 to 1.1)	0.9 (-0.5 to 2.2)	-1.5 (-3.2 to 0.3)	-1.4 (-3.3 to 0.4)
	Affective, score	-0.9 (-1.8 to 0.0)	-0.3 (-1.2 to 0.7)	0.3 (-0.7 to 1.3)	-0.3 (-1.3 to 0.8)	-1.2 (-2.5 to 0.1)	-0.0 (-1.4 to 1.4)
Phys Activity	Steps per day, n	79 (-263 to 422)	158 (-229 to 544)	-266 (-650 to 117)	345 (-87 to 777)	346 (-169 to 860)	-188 (-768 to 392)
	Total EE/day, kcal	-37 (-116 to 42)	-53 (-141 to 36)	25 (-63 to 113)	-55 (-155 to 45)	-63 (-181 to 56)	3 (-131 to 137)
	Sedentary, m/day	6 (-26 to 37)	5 (-30 to 40)	-6 (-41 to 29)	-5 (-44 to 34)	12 (-36 to 59)	10 (-42 to 63)
	Light: m/day	-27 (-48 to 7)	-2 (-25 to 21)	-23 (-46 to -1)	3 (-23 to 28)	-4 (-35 to 27)	-5 (-39 to 30)
	Moderate: m/day	3 (-3 to 8)	-3 (-10 to 3)	-0 (-7 to 6)	-2 (-9 to 6)	3 (-6 to 11)	-1 (-11 to 8)
	Vigorous: m/day	-1 (-2 to 0)	-1 (-3 to -0)	0 (-1 to 2)	-0 (-2 to 1)	-1 (-3 to 1)	-1 (-3 to 1)

Data presented as mean and 95% CIs adjusted for baseline values. *significant within group difference from baseline # significant between group difference.
CRQ: chronic respiratory disease questionnaire; EE: energy expenditure; ESWT: endurance shuttle walk test; Funct: Function; ISWT: incremental shuttle walk test; Isotime: comparison of isotime scores at baseline and end training; METs: metabolic equivalents; m/day: minutes per day; n: number; Phys: physical; RPE: rate of perceived exertion; Sedentary: awake time spent METs <1.5; Light Activity: time spent METs 1.5 to <3; Moderate Activity: Time spent METs 3 to <6; Vigorous Activity: time spent METs ≥6.